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SYNTHESIS OF SOME NEW BIHETEROCYCLES BY A ONE-POT SUZUKI-MIYaura COUPLING REACTION

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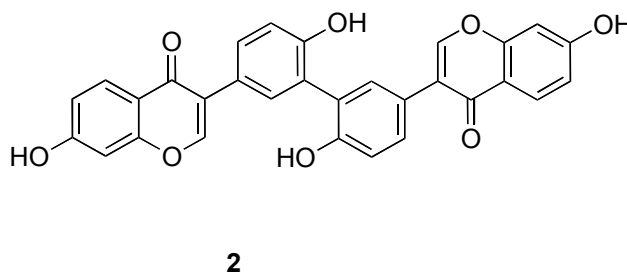
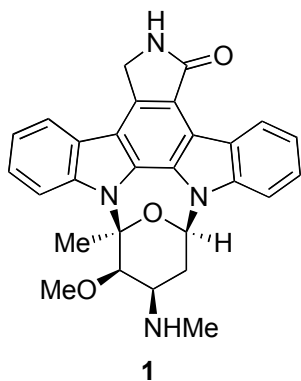
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Dedicated to Prof. Akira Suzuki on the occasion of his 80th birthday

Abstract – Halogenated indoles, benzofurans and flavones were subjected to a one-pot Suzuki-Miyaura coupling reaction to generate a series of new biheterocycles. The methodology may be readily adapted to the synthesis of a wide variety of substituted biheterocycles.

INTRODUCTION

Biheterocyclic compounds display a wide range of biological activities, and in many cases enhanced activity is observed compared to the single parent heterocycle.¹ Indole-containing biheterocycles have received considerable attention due to their presence in natural products such as melanin pigment and staurosporine **1**, an alkaloid with potent biological activities.²



Biindoles can also act as ligands in transition metal complexes, and thus have the potential to find key use in catalytic processes.³ However, biindoles linked *via* aryl groups at C2 or C3 have not been reported in

the literature. The related bibenzofurans containing an aryl group linkage have been used as optical brighteners and fluorescent agents for textiles and cosmetic compositions.⁴ Biflavonoids are plant secondary metabolites and to date more than 100 biflavonoids have been isolated from various plants sources. The naturally occurring biisoflavonoid kudzuiflavone **A 2** contains an aryl-aryl linkage,⁵ however the corresponding biflavonoid compound has not been found in Nature. The biological activities of biflavonoids have been extensively studied.^{6,7}

Intrigued by the wide range of useful properties associated with biheterocycles, and in continuation of our interest in the synthesis of novel heterocyclic systems, we set out to synthesize symmetrically linked biindoles, bibenzofurans and biflavones with special emphasis on coupling through a pendant aryl group to create a biaryl linkage.

RESULTS AND DISCUSSION

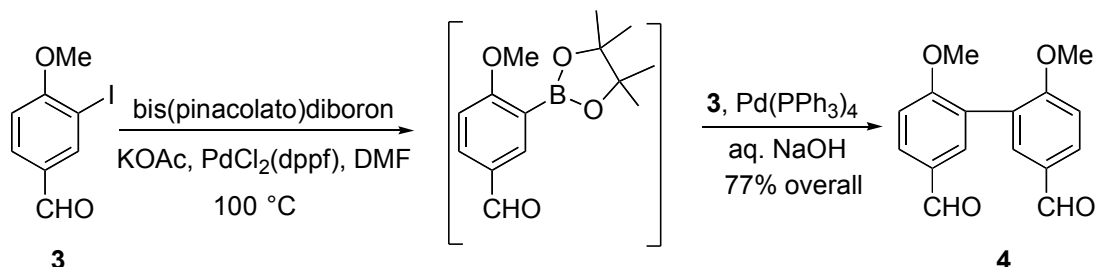
A variety of methods have been reported for the synthesis of biheterocycles and their analogues. Our group has previously described the facile one-step synthesis of biindolyls using indolone and phosphoryl chloride as the Vilsmeier reagent.⁸ We envisaged that the Suzuki-Miyaura coupling reaction could be utilized for the synthesis of biheterocycles. The Suzuki-Miyaura reaction involves the palladium-catalyzed coupling of an organoboron compound with an organohalide, and is one of the most extensively used reactions in the synthesis of natural products, pharmaceuticals and advanced materials.⁹⁻¹⁴ One major advantage of the Suzuki-Miyaura reaction is that only a catalytic amount of palladium catalyst is needed, whereas other coupling methodologies usually require stoichiometric amounts of metal catalyst (*e.g.* copper).

A one-pot Suzuki-Miyaura coupling reaction has been reported, and involves *in situ* conversion of an aryl halide into a boronate ester intermediate followed by the addition of a second equivalent of aryl halide together with a palladium catalyst and base to afford the biaryl product.¹⁵⁻²⁰ Isolation of the arylboronate intermediates is not required, circumventing the need for large volumes of solvents and reducing the time required for reaction. This method is particularly useful in cases where the boronate intermediate is unstable. In order to carry out the two steps in one-pot effectively, the boronate ester formation needs to be reasonably clean. Furthermore, a judicious selection of reaction conditions, such as catalyst, solvent, base and temperature is also essential.

The Suzuki-Miyaura reaction was therefore applied to readily available 4-haloaryl substituted indoles, benzofurans, and flavones, as well as to 4-, 5-, 6-, and 7-bromoindoles themselves. Recently, a Suzuki-Miyaura coupling reaction has been reported for the synthesis of homo- and hetero-biindoles.²¹

In our work, the reaction conditions were optimized using 3-iodo-4-methoxybenzaldehyde **3** as the substrate by treating it with bis(pinacolato)diboron in the presence of PdCl₂(dppf) and potassium acetate

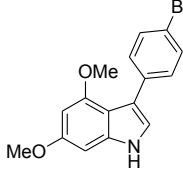
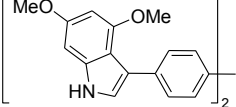
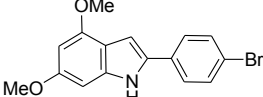
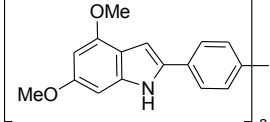
in dry DMF. Upon complete conversion of the aryl halide into the boronate intermediate (TLC analysis), another equivalent of iodobenzaldehyde **3** was added followed by the addition of $\text{Pd}(\text{PPh}_3)_4$ (found to improve the yield) and aqueous sodium hydroxide solution. After work-up and chromatographic purification, biphenyl **4** was obtained in 77% yield (Scheme 1).

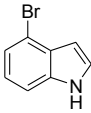
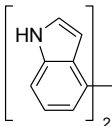
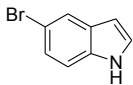
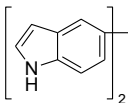
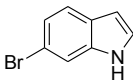
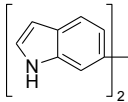
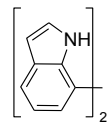
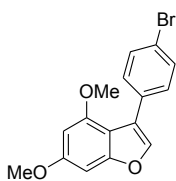
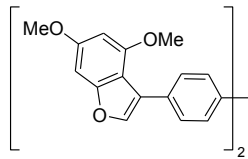
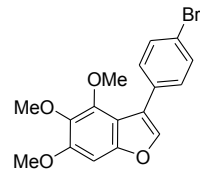
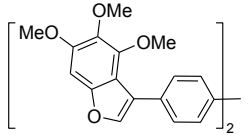
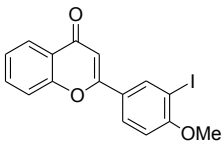
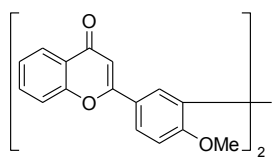
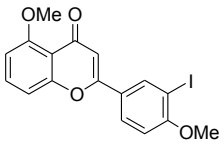
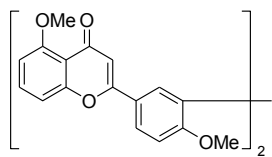


Scheme 1. Synthesis of 2,2'-dimethoxydiphenyl-5,5'-dicarbaldehyde **4**

Encouraged by this result, the same methodology was applied for the preparation of directly linked biindolyis, as well as biindoles, bibenzofurans and biflavones linked *via* a biphenyl moiety. When 3-(4-bromophenyl)-4,6-dimethoxyindole **5** was subjected to the one-pot reaction conditions described above, the resulting dimer **15** was obtained in 37% yield. In the ^1H NMR spectrum of the dimer, the protons for the pendant phenyl ring appeared as two doublets at δ 7.67 and 7.69 ppm, while in the starting material these protons resonated as a singlet at δ 7.46 ppm. The structure of the dimer was further confirmed by the presence of the molecular ion peak at m/z 504 in the mass spectrum. The coupling reaction of other bromoindoles **6-10** and bromobenzofurans **11-12** proceeded in a similar manner to yield the corresponding biindoles **16-20** and bibenzofurans **21-22** respectively in moderate (but not optimized) yields of 36-50% (Table 1).

Table 1. Syntheses of biheterocycles *via* a one-pot Suzuki-Miyaura coupling reaction

Entry	Substrate	Product	Yield (%)
1	 5	 15	37
2	 6	 16	36

3	7		17		41
4	6		18		37
5	9		19		44
6	10		20		50
7	11		21		42
8	12		22		39
9	13		23		63
10	14		24		59

3'-Iodoflavones were chosen as the substrates for the synthesis of biflavones due to the ease of their preparation from the corresponding iodobenzaldehydes. The coupling reaction was found to be more facile with iodoflavones **13-14**, requiring only 3-4 h at 100 °C for completion, and resulting in higher yields of the corresponding dimers **23-24** (59-63%). The formation of the coupling products was confirmed by ^1H and ^{13}C NMR spectroscopy, IR and UV spectroscopy, mass spectrometry and elemental analyses. Known products were characterized by comparison of their ^1H NMR spectra and melting points with those reported in the literature.

In conclusion, we have achieved a one-pot synthesis of biindoles, bibenzofurans and biflavones linked by

a biaryl moiety, and directly linked biindolyls. The described methodology represents an efficient access to afford a range of biheterocycles and their analogues with potentially interesting biological activities.

EXPERIMENTAL

All reactions were performed under an argon atmosphere. Melting points are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer EA 1108. NMR spectra were recorded in the designated solvents on a Bruker Avance DPX300 (300 MHz) spectrometer and were internally referenced to the solvent peaks. Low resolution mass spectrometric analysis was carried out on a Q-Star Pulsar API (Applied Biosystems) mass spectrometer. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR spectrometer. Ultraviolet-visible spectra were recorded using a Varian Cary 100 Scan spectrometer. Column chromatography was carried out using Merck 230-400 mesh ASTM silica gel.

General procedure for one-pot Suzuki-Miyaura synthesis: A mixture of aryl halide (0.5 mmol), $\text{PdCl}_2(\text{dppf})$ (20 mg, 0.025 mmol), bis(pinacolato)diboron (127 mg, 0.5 mmol) and potassium acetate (180 mg, 1.8 mmol) in dry DMF (2 mL) was heated under argon at 100 °C for 2-3 h. Another equivalent of aryl halide (0.5 mmol) was added followed by addition of $\text{Pd}(\text{PPh}_3)_4$ (25 mg, 0.04 mmol), and solution of NaOH (40 mg, 1 mmol) in water (0.4 mL). The reaction was continued further (4 h for aryl iodides and 12 h for bromides) cooled to rt, diluted with water (50 mL) and stirred for 10 min. The product was filtered, washed with water (25 mL), air dried and purified by silica gel column chromatography.

2,2'-Dimethoxydiphenyl-5,5'-dicarbaldehyde (4): An off-white solid (77%). Purified by silica gel column chromatography [eluted initially with dichloromethane and then with dichloromethane – EtOAc (90:10)]. Mp 131-133 °C (lit.,²² 134 °C); ^1H NMR (300 MHz, CDCl_3): δ 3.86 (6H, s, $2 \times \text{CH}_3\text{O}$), 7.09 (2H, d, $J = 8.3$ Hz, H3, H3'), 7.77 (2H, d, $J = 2.3$ Hz, H6, H6'), 7.91 (2H, dd, $J = 2.3, 8.3$ Hz, H4, H4'), 9.92 (2H, s, $2 \times \text{CHO}$).

4,4'-Bis(4,6-dimethoxyindol-3-yl)biphenyl (15): An off-white solid (37%). Purified by silica gel column chromatography [eluted with hexane – EtOAc (50:50)]. Mp 291-294 °C; UV (MeOH): λ_{max} 206 (ϵ 41775 $\text{cm}^{-1}\text{M}^{-1}$), 224 (ϵ 41595 $\text{cm}^{-1}\text{M}^{-1}$), 324 (ϵ 19084 $\text{cm}^{-1}\text{M}^{-1}$) nm; IR (KBr): ν_{max} 3413, 3348, 1624, 1545, 1334, 1214, 1162, 1143 cm^{-1} ; ^1H NMR (300 MHz, acetone- d_6): δ 3.80 (6H, s, $2 \times \text{CH}_3\text{O}$), 3.83 (6H, s, $2 \times \text{CH}_3\text{O}$), 6.25 (2H, d, $J = 1.9$ Hz, H5, H5''), 6.61 (2H, d, $J = 1.9$ Hz, H7, H7''), 7.22 (2H, m, H2, H2''), 7.67 and 7.69 (8H, $2 \times$ d, $J = 8.7$ Hz, H2', H2''', H3', H3''', H5', H5''', H6, H6'''), 10.23 (2H, bs, $2 \times \text{NH}$); ^{13}C NMR (75.6 MHz, acetone- d_6): δ 54.3, 54.7, 87.1, 91.8, 117.6, 117.7, 120.9, 121.0, 125.4, 129.6, 135.6, 137.6, 154.7, 157.5; MS (ESI) m/z for $\text{C}_{32}\text{H}_{28}\text{N}_2\text{O}_4$ (M^+) 504.17; Anal. Calcd for $\text{C}_{32}\text{H}_{28}\text{N}_2\text{O}_4$: C, 76.17; H, 5.59; N, 5.55. Found: C, 76.51; H, 5.72; N, 5.32.

4,4'-Bis(4,6-dimethoxyindol-2-yl)biphenyl (16): An off-white solid (36%). Purified by silica gel column chromatography [eluted with hexane – EtOAc (50:50)]. Mp 220 °C; UV (MeOH): $\lambda_{\max}$ 215 (ϵ 52808 cm⁻¹M⁻¹), 258 (ϵ 23419 cm⁻¹M⁻¹), 366 (ϵ 44757 cm⁻¹M⁻¹) nm; IR (KBr): $\nu_{\max}$ 2933, 2836, 1623, 1602, 1275, 1217, 1149, 1127, 797 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆): δ 3.79 (6H, s, 2 × CH₃O), 3.91 (6H, s, 2 × CH₃O), 6.20 (2H, d, *J* = 1.9 Hz, H5, H5'), 6.56 (2H, d, *J* = 1.1 Hz, H3, H3'), 6.89 (2H, d, *J* = 1.9 Hz, H7, H7'), 7.76 and 7.87 (8H, 2 × d, *J* = 8.3 Hz, H2', H2'', H3', H3'', H5', H5'', H6', H6''), 10.52 (2H, bs, 2 × NH); ¹³C NMR (75.6 MHz, acetone-*d*₆): δ 54.5, 54.7, 86.8, 91.4, 96.6, 114.5, 124.7, 126.8, 131.9, 134.6, 138.3, 138.9, 153.6, 157.9; MS (MALDI-ESI) *m/z* Calcd for C₃₂H₂₈N₂O₄ (M)⁺ 504.57. Found 504.12; Anal. Calcd for C₃₂H₂₈N₂O₄: C, 76.17; H, 5.59; N, 5.55. Found: C, 76.35; H, 5.82, N, 5.50.

4,4'-Biindolyl (17): Grey crystals (41%). Purified by silica gel column chromatography [eluted with hexane – EtOAc (80:20)]. Mp 258-260 °C; UV (MeOH): $\lambda_{\max}$ 219 (ϵ 31918 cm⁻¹M⁻¹), 300 (ϵ 13800 cm⁻¹M⁻¹); IR (KBr): $\nu_{\max}$ 3395, 1426, 1403, 1333, 758 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.60 (2H, dd, *J* = 0.8, 1.9 Hz, H3, H3'), 7.17-7.56 (8H, m, H2, H2', H5, H5', H6, H6', H7, H7'), 8.23 (2H, bs, 2 × NH); ¹³C NMR (75.6 MHz, CDCl₃): δ 103.1, 109.8, 120.6, 122.0, 123.7, 126.8, 133.8, 136.2; HRMS (TOF-ESI) *m/z* Calcd for C₁₆H₁₂N₂Na (M + Na)⁺ 255.0893. Found 255.1544; Anal. Calcd for C₁₆H₁₂N₂: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.31; H, 5.40, N, 11.84.

5,5'-Biindolyl (18): Grey crystals (37%). Purified by silica gel column chromatography [eluted with hexane – EtOAc (80:20)]. Mp 214 °C, (lit., ²³ 212-215 °C); IR (KBr): $\nu_{\max}$ 3396, 1465, 1454, 1416, 1027, 875, 804, 730 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆): δ 6.50 (2H, m, H3, H3'), 7.30-7.50 (6H, m, H2, H2', H6, H6', H7, H7'), 7.80 (2H, s, H4, H4'), 10.18 (2H, bs, 2 × NH); ¹³C NMR (75.6 MHz, acetone-*d*₆): δ 101.7, 111.2, 118.4, 121.3, 124.9, 125.0, 128.7, 134.1.

6,6'-Biindolyl (19): Grey needles (44%). Purified by silica gel column chromatography [eluted with hexane – EtOAc (70:30)]. Mp 285 (dec); UV (MeOH): $\lambda_{\max}$ 211 (ϵ 33037 cm⁻¹M⁻¹), 243 (ϵ 47980 cm⁻¹M⁻¹), 304 (ϵ 27387 cm⁻¹M⁻¹) nm; IR (KBr): $\nu_{\max}$ 3385, 1453, 1096, 1061, 807, 722, 528 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆): δ 6.46 (2H, m, H3, H3'), 7.32 (2H, m, H2, H2'), 7.36 (2H, dd, *J* = 1.9, 8.3 Hz, H5, H5'), 7.61 (2H, d, *J* = 8.3 Hz, H4, H4'), 7.69 (2H, m, H7, H7'); ¹³C NMR (75.6 MHz, acetone-*d*₆): δ 101.2, 109.4, 119.1, 120.2, 124.8, 127.0, 136.1, 137.0; HRMS (TOF-ESI) *m/z* Calcd for C₁₆H₁₂N₂Na (M + Na)⁺ 255.0893. Found 255.1547; Anal. Calcd for C₁₆H₁₂N₂: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.30; H, 5.35; N, 11.72.

7,7'-Biindolyl (20): Grey crystals (50%). Purified by silica gel column chromatography [eluted with hexane – EtOAc (70:30)]. Mp 252 °C (lit., ²⁴ 244-245 °C); UV (MeOH): $\lambda_{\max}$ 217 (ϵ 28529 cm⁻¹M⁻¹), 293 (ϵ 13086 cm⁻¹M⁻¹) nm; IR (KBr): $\nu_{\max}$ 3389, 1423, 1410, 1337, 804, 779, 728 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆): δ 6.54 (2H, m, H3, H3'), 7.13 (2H, dd, *J* = 7.1, 7.5 Hz, H5, H5'), 7.25 (2H, dd, *J* = 1.1, 7.1 Hz, H6, H6'), 7.29 (2H, m, H2, H2'), 7.61 (2H, dd, *J* = 1.1, 7.5 Hz, H4, H4'), 9.91 (2H, bs, 2 × NH); ¹³C

NMR (75.6 MHz, acetone- d_6): δ 101.8, 119.4, 119.6, 121.6, 122.7, 125.1, 128.8, 134.1.

4,4'-Bis-(4,6-dimethoxybenzofuran-3-yl)biphenyl (21): A white solid (42%). Purified by silica gel column chromatography [eluted with hexane – EtOAc (80:20)]. Mp 232-235 °C; UV (MeOH): $\lambda_{\max}$ 212 (ϵ 93646 $\text{cm}^{-1}\text{M}^{-1}$), 260 (ϵ 54888 $\text{cm}^{-1}\text{M}^{-1}$), 298 (ϵ 40444 $\text{cm}^{-1}\text{M}^{-1}$) nm; IR (KBr): $\nu_{\max}$ 1623, 1592, 1500, 1333, 1165, 1147, 1093, 1084 cm^{-1} ; ^1H NMR (300 MHz, acetone- d_6): δ 3.87 (12H, s, $2 \times \text{CH}_3\text{O}$), 6.46 (2H, d, $J = 1.9$ Hz, H7, H7''), 6.77 (2H, d, $J = 1.9$ Hz, H5, H5''), 7.76 (8H, s, H2', H2''', H3', H3''', H5', H5''', H6', H6'''), 7.80 (2H, s, H2, H2''); ^{13}C NMR (75.6 MHz, acetone- d_6): δ 54.8, 55.0, 88.2, 94.5, 118.3, 122.3, 126.0, 129.5, 131.4, 139.1, 140.2, 145.2, 154.6, 158.0, 159.6; MS (ESI) m/z for $\text{C}_{32}\text{H}_{26}\text{O}_6$ ($\text{M}+1$) $^+$ 507.16; Anal. Calcd for $\text{C}_{32}\text{H}_{26}\text{O}_6$: C, 75.88; H, 5.17. Found: C, 75.88; H, 5.17.

4,4'-Bis-(4,5,6-trimethoxybenzofuran-3-yl)biphenyl (22): A white solid (39%). Purified by silica gel column chromatography [eluted with hexane – EtOAc (65:35)]. Mp 206-208 °C; UV (MeOH): $\lambda_{\max}$ 209 (ϵ 82879 $\text{cm}^{-1}\text{M}^{-1}$), 257 (ϵ 39939 $\text{cm}^{-1}\text{M}^{-1}$), 293 (ϵ 47836 $\text{cm}^{-1}\text{M}^{-1}$) nm; IR (KBr): $\nu_{\max}$ 2962, 2937, 1614, 1569, 1469, 1195, 1121 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 3.70 (6H, s, $2 \times \text{CH}_3\text{O}$), 3.91 (6H, s, $2 \times \text{CH}_3\text{O}$), 3.93 (6H, s, $2 \times \text{CH}_3\text{O}$), 6.90 (2H, s, H7, H7''), 7.59 (2H, s, H2, H2''), 7.74 (8H, m, H2', H2''', H3', H3''', H5', H5''', H6', H6''); ^{13}C NMR (75.6 MHz, CDCl_3): δ 56.2, 61.4, 61.6, 91.5, 112.9, 122.3, 126.6, 129.3, 131.0, 138.9, 139.5, 140.6, 147.1, 152.4, 152.7; MS (MALDI-ESI) m/z Calcd for $\text{C}_{34}\text{H}_{30}\text{O}_8$ (M) $^+$ 566.59. Found 566.19; Anal. Calcd for $\text{C}_{34}\text{H}_{30}\text{O}_8$: C, 72.07; H, 5.34. Found: C, 72.37; H, 5.50.

4',4'''-Dimethoxy-3',3'''-biflavone (23): A pale yellow solid (63%). Purified by silica gel column chromatography [eluted with CH_2Cl_2 – EtOAc (70:30)]. Mp 322 °C, (lit.,²⁵ 327 °C); IR (KBr): $\nu_{\max}$ 1653, 1605, 1465, 1493, 1269, 1248 cm^{-1} ; ^1H NMR (300 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$): δ 3.81 (6H, s, 4' CH_3O , 4''' CH_3O), 6.74 (2H, s, H3, H3''), 7.08 (2H, d, $J = 9.0$ Hz, H5', H5''), 7.35 (2H, td, $J = 1.4, 7.9$ Hz, H6, H6''), 7.51 (2H, dd, $J = 1.1, 7.9$ Hz, H8, H8''), 7.63 (2H, ddd, $J = 1.5, 7.9, 8.3$ Hz, H7, H7''), 7.81 (2H, d, $J = 2.6$ Hz, H2', H2'''), 7.94 (2H, dd, $J = 2.6, 9.0$ Hz, H6', H6''), 8.12 (2H, dd, $J = 1.5, 7.9$ Hz, H5, H5''); ^{13}C NMR (75.6 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$): δ 55.8, 105.8, 111.3, 117.9, 123.5, 125.2, 125.2, 127.4, 127.9, 129.4, 133.8, 156.1, 160.0, 163.9, 179.0; MS (ESI) m/z for $\text{C}_{32}\text{H}_{22}\text{O}_6\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 525.11.

4',4''',5,5''-Tetramethoxy-3',3'''-biflavone (24): A pale yellow solid (59%). Purified by silica gel column chromatography [eluted with CH_2Cl_2 – EtOAc (70:30)]. Mp 321-323 °C; UV (MeOH): $\lambda_{\max}$ 209 (ϵ 29995 $\text{cm}^{-1}\text{M}^{-1}$), 264 (ϵ 23149 $\text{cm}^{-1}\text{M}^{-1}$), 328 (ϵ 28283 $\text{cm}^{-1}\text{M}^{-1}$) nm; IR (KBr): $\nu_{\max}$ 1633, 1601, 1475, 1262, 1102, 1023, 803 cm^{-1} ; ^1H NMR (300 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$): δ 3.84 (6H, s, 4' CH_3O , 4''' CH_3O), 3.96 (6H, s, 5 CH_3O , 5'' CH_3O), 6.72 (2H, s, H3, H3''), 6.80 (2H, d, $J = 8.3$ Hz, H6, H6''), 7.09 (2H, d, $J = 8.3$ Hz, H5', H5''), 7.11 (2H, d, $J = 8.3$ Hz, H8, H8''), 7.52 (2H, t, $J = 8.3$ Hz, H7, H7''), 7.80 (2H, d, $J = 1.9$ Hz, H2', H2'''), 7.92 (2H, dd, $J = 1.9, 8.3$ Hz, H6', H6''); ^{13}C NMR (75.6 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$): δ 55.8, 56.1, 106.4, 107.4, 110.0, 111.2, 114.1, 123.2, 127.4, 127.6, 129.2, 133.8, 158.1, 159.6, 159.8, 161.6, 178.9; MS (ESI) m/z for $\text{C}_{34}\text{H}_{26}\text{O}_8\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 585.12; Anal. Calcd for $\text{C}_{34}\text{H}_{26}\text{O}_8 \cdot 2\text{H}_2\text{O}$: C, 68.22; H,

5.05. Found: C, 68.19; H, 4.85.

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